(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 December 2002 (05.12.2002)

PCT

(10) International Publication Number
WO 02/096878 A1

(51) International Patent Classification[7]: C07D 213/70

(21) International Application Number: PCT/US02/17027

(22) International Filing Date: 30 May 2002 (30.05.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/871,429 31 May 2001 (31.05.2001) US

(71) Applicant *(for all designated States except US)*: **NORTH CAROLINA STATE UNIVERSITY** [US/US]; 2401 Research Drive, Campus Box 8210, Raleigh, NC 27695-8210 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **COMINS, Daniel, L.** [US/US]; 108 Canderstone Court, Raleigh, NC 27606 (US). **HUANG, Shenlin** [CN/US]; 425 Parsonage Road, Edison, NJ 08337 (US).

(74) Agent: **MYERS BIGEL SIBLEY & SAJOVEC**; PO Box 37428, Raleigh, NC 27627 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/096878 A1

(54) Title: A SHORT SYNTHESIS OF PYRIDINE-BASED PHARMACEUTICAL INTERMEDIATES WITH SULFUR-CONTAINING GROUPS AT THE 2- AND 3-POSITIONS

(57) Abstract: A method of making a compound of Formula VI:wherein Tr is a triphenyl group; R1, R2 and R3 are each independently selected from the group consisting of H, C1-C4 alkyl, C1-C4 alkoxy, aryl, heteroaryl, and arylalkyl; R4 is C2-C6 alkyl, and R5 and R6 are each independently H or C1-C4 alkyl, involves the step of reacting a compound of Formula V: with Tr-OH to produce a compound of Formula VI. The compounds of Formula VI are useful as intermediates in the manufacture of antibiotic agents. Methods of making compounds of Formula V, and intermediates made or used in the foregoing methods, are also described.

A SHORT SYNTHESIS OF PYRIDINE-BASED PHARMACEUTICAL INTERMEDIATES WITH SULFUR-CONTAINING GROUPS AT THE 2- AND 3-POSITIONS

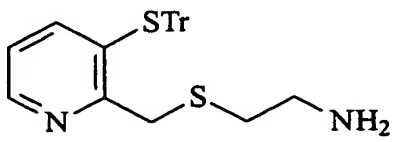
Field of the Invention

The present invention concerns methods for the synthesis of pyridine-based compounds, which compounds are useful as intermediates for the manufacture of pharmaceutical compounds.

Background of the Invention

Over the past three decades a large variety of antibiotics have become available for clinical use. Unfortunately, the wide-spread use of these antibiotics has caused a rapid increase in the number of bacterial strains that are resistant to the currently available antibiotics.

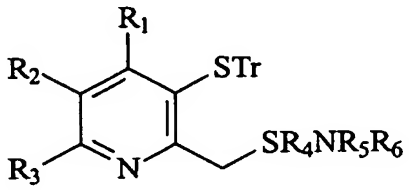
S. Hecker et al., PCT Application WO 01/21623 (published 29 March 2001), describes 7-acylamino-3-heteroarylthio-3-cephem carboxylic acid antibiotics and prodrugs thereof. The compounds described therein are active as antibiotics against a wide spectrum of organisms including organisms which are resistant to beta-lactam antibiotics. However, the compounds described therein are complicated, and require the synthesis of a variety of separate groups. One group which must be synthesized to make these compounds is the C3 side-chain, an intermediate for which is illustrated on page 51 therein as follows:



However, the synthesis of such C3 side chain groups as set forth in S. Hecker et al. requires in excess of 6 steps (see pages 49-52 therein). Accordingly, there is a need for new ways to make the intermediates used to make the antibiotic compounds described in S. Hecker et al.

Summary of the Invention

Accordingly, a first aspect of the present invention is a method of making a compound of **Formula VI:**



(VI)

wherein:

Tr is a triphenyl group;

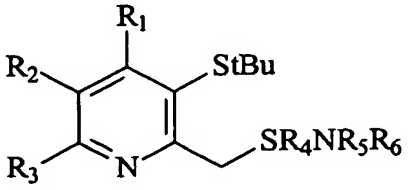
R_1, R_2 and R_3 are each independently selected from the group consisting of H, C1-C4 alkyl, C1-C4 alkoxy, aryl, heteroaryl, and arylalkyl;

R_4 is C2-C6 alkyl, and

R_5 and R_6 are each independently H or C1-C4 alkyl,

comprising:

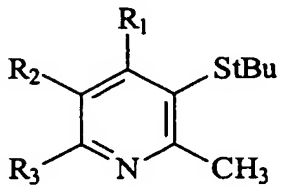
reacting a compound of **Formula V**:



(V)

with Tr-OH to produce a compound of **Formula VI.**

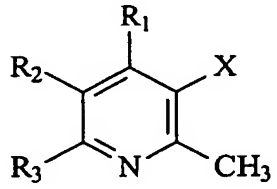
A second aspect of the present invention is a method of making a compound of **Formula V** as described above, the method comprising reacting a compound of **Formula IV:**



(IV)

where tBu is *tert*-Butyl or other suitable leaving group, with $R_6R_5NR_4SSR_4NR_5R_6$ in the presence of a strong amide base to produce a compound of **Formula V.**

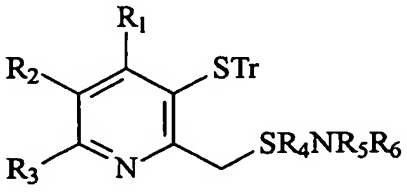
A third aspect of the present invention is a method of a compound of **Formula IV** as described above, comprising reacting a compound of **Formula III:**



(III)

wherein X is halogen, with sodium *tert*-butylthiolate or potassium *tert*-butylthiolate to produce a compound of **Formula IV.**

A fourth aspect of the present invention is a compound of **Formula VI:**



(VI)

wherein:

Tr is a triphenyl group;

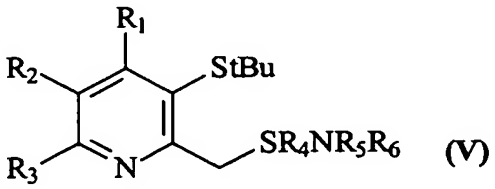
R_1, R_2 and R_3 are each independently selected from the group consisting of H, C1-C4 alkyl, C1-C4 alkoxy, aryl, heteroaryl, and arylalkyl;

R_4 is C2-C6 alkyl, and

R_5 and R_6 are each independently H or C1-C4 alkyl;

subject to the proviso that *(i)* R_1, R_2 and R_3 are not all simultaneously H, or *(ii)* R_4 is not C2, or *(iii)* R_5 and R_6 are not simultaneously H.

A further aspect of the present invention is a compound of **Formula V**:



(V)

wherein:

tBu is *tert*-butyl, or other suitable leaving group;

R_1, R_2 and R_3 are each independently selected from the group consisting of H, C1-C4 alkyl, C1-C4 alkoxy, aryl, heteroaryl, and arylalkyl;

R_4 is C2-C6 alkyl, and

R_5 and R_6 are each independently H or C1-C4 alkyl.

Compounds of Formula VI above are useful as intermediates in the manufacture of antibiotic compounds.

Compounds of Formula V above are useful as intermediates in the manufacture of compounds of Formula VI.

The foregoing and other objects and aspects of the present invention are explained in greater detail in the specification set forth below.

Detailed Description of Preferred Embodiments

"Alkyl" as used herein refers to linear or branched alkyl, preferably linear alkyl, including but not limited to methyl, ethyl, propyl, and butyl (Bu).

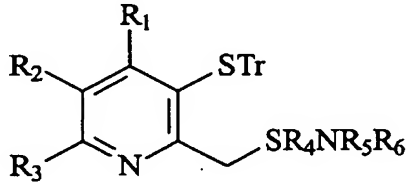
"Halo" as used herein refers to any suitable halogen group, such as fluoro, chloro, bromo, or iodo.

"Aryl" as used herein refers to any suitable aromatic group, such as phenyl, which aromatic group may be substituted or unsubstituted.

"Arylalkyl" as used herein refers to any suitable aryl group covalently coupled to an alkyl group, such as benzyl.

"Triphenyl" or "Tr" groups as used herein may be unsubstituted or substituted one or more times by additional groups such as C1-C4 alkyl, C1-C4 alkyloxy, or halo. Para substitutions are preferred, but substitutions may be of any number from 1 to 5 and in any position, with mono or di substitutions preferred.

As noted above, a first aspect of the present invention is a method of making a compound of **Formula VI:**



(VI)

wherein:

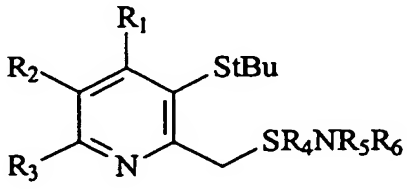
Tr is a triphenyl group;

R_1, R_2 and R_3 are each independently H C1-C4 alkyl, C1-C4 alkoxy, aryl, heteroaryl, or arylalkyl (preferably H),

R_4 is C2-C6 alkyl (preferably C2), and

R5 and R_6 are each independently H or C1-C4 alkyl (preferably H).

The method comprises reacting a compound of **Formula V:**

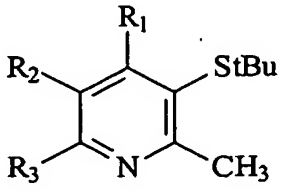


(V)

with Tr-OH to produce a compound of **Formula VI**. The reacting step is may be carried out as a one-pot, two step reacting step. The reaction step is preferably carried out in the presence of a strong organic acid, examples including but not limited to methanesulfonic acid and arylsulfonic acid (*e.g.*, paratoluene sulfonic acid). The reacting step is typically carried out in a polar solvent such as acetic acid, which solvent is preferably non-aqueous, and may be carried out at any suitable temperature such as at room temperature.

Compounds of **Formula VI** are useful, among other things, as C-3 side chain intermediates useful for the production of 7-acylamino-3-heterarylthio-3-cephem carboxylic acid antibiotics, and prodrugs thereof, as shown in S. Hecker et al., PCT Application WO 01/21623 (29 March 2001) (see pages 49-50). Particularly organisms for which the compounds of the invention may be used as antibiotics include but are not limited to *Staphylococcus aureus, Enterobacteriaceae,* and *Pseudomonas*. The compounds may be used *in vivo* as a pharmaceutical agent by (for example), oral, parenteral, or topical administration, or may be used *in vitro*, for example as a topical or surface antibiotic.

A compound of **Formula V** above may be produced by reacting a compound of **Formula IV**:

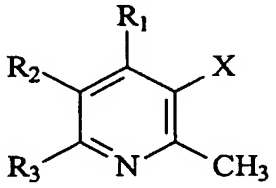


(IV)

with $R_6R_5NR_4SSR_4NR_5R_6$ (which may be produced in accordance with known techniques), preferably in the presence of a strong amide base, to produce a compound of **Formula V**. This reacting step may be carried out in any suitable solvent, typically an etherial solvent such as dialkyl ether (e.g., diethyl ether), dimethoxyethane, tetrahydrofuran, or mixtures thereof. Any suitable strong amide base may be used, such as lithium, sodium, and potassium amide bases. Any suitable amide may be used, such as

a dialkyl amide (*e.g.*, diethyl amide). The temperature at which the reacting step is carried out is not critical, but is preferably less than room temperature (*e.g.*, from –80 to –20 or even 0 degrees centigrade).

The compound of **Formula IV** above may be produced by reacting a compound of **Formula III:**



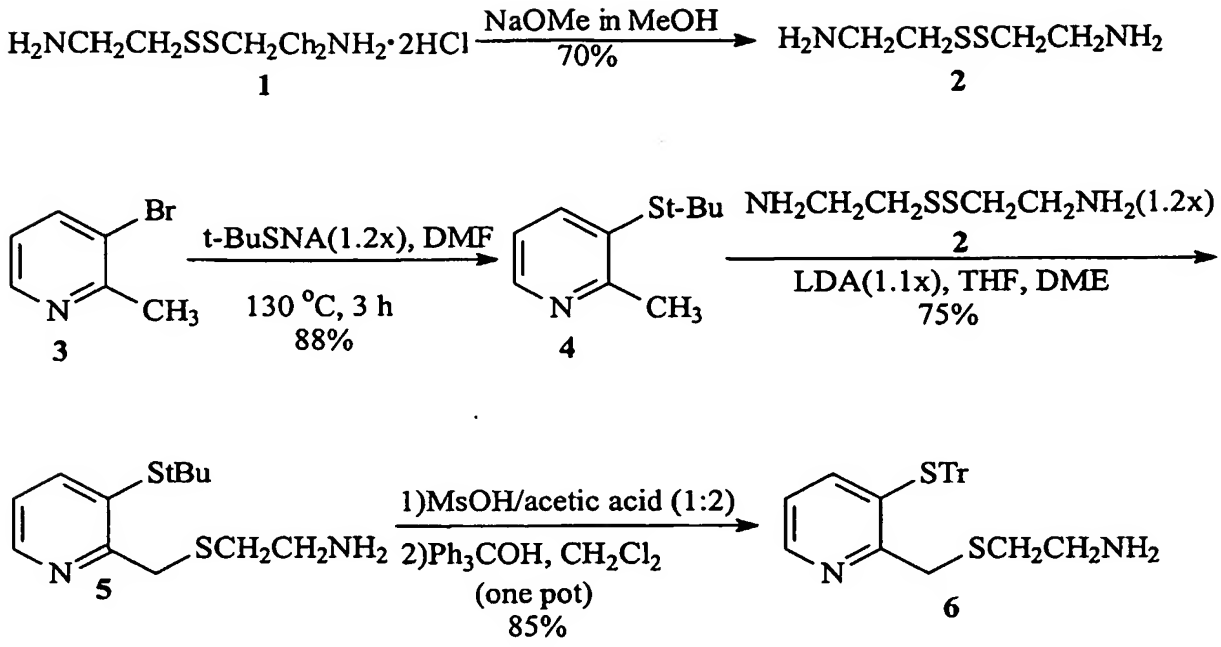
(III)

wherein X is halogen, with sodium *tert*-butylthiolate or potassium *tert*-buthylthiolate to produce a compound of **Formula IV.** This reacting step may be carried out in any suitable solvent, preferably nonaqueous, such as a polar aprotic solvent (*e.g.*, dimethylformamide and/or dimethylsulfoxide). The reacting step may be carried out at any suitable temperature, such as from 20 to 120 or 130 degrees centigrade. Compounds of Formula III are known or may be prepared in accordance with known techniques.

The present invention is explained in greater detail in the following non-limiting examples.

EXAMPLES 1-4

Examples 1 to 4 below illustrate the set of reactions shown in **Scheme 2** below.



Scheme 2

EXAMPLE 1

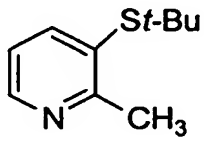
Cystamine (2)

$H_2NCH_2CH_2SSCH_2CH_2NH_2$

To a suspension of cystamine dihydrochloride **(1)** (10.0 g, 44.4 mmol) in anhydrous methanol (20 mL) was added NaOMe (20 mL, 88.8 mmol, 25 wt. % solution in methanol) slowly. The mixture was stirred for 0.5 h and then filtered through a fritted funnel. The solvent was removed *in vacuo* without heating (caution: heating the solution can cause decomposition of cystamine). The residue was dissolved in diethyl ether and then filtered. The filtrate was concentrated *in vacuo* and the residue was bulb-to-bulb distilled (120 °C, 0.5 mmHg) to afford 4.8 g (70%) of the desired product **2** as a colorless liquid. The oil was dissolved in DME and used directly in the next step.

EXAMPLE 2

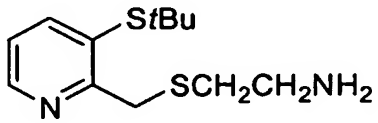
3-*tert*-Butylsulfanyl-2-methylpyridine (4)



To a solution of 3-bromo-2-methyl-pyridine **(3)** (15.0 g, 87.1 mmol) in DMF (100 mL) was added sodium *tert*-butylthiolate (11.7 g, 104.5 mmol) under N_2. The mixture was heated to 130 °C for 3 h. After cooling, it was poured into EtOAc (200 mL) and washed with water (3 × 100 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was bulb-to-bulb distilled (90 °C, 0.5 mmHg) to afford 13.9 g (88%) of the desired product as a colorless liquid. FTIR (thin film) 2962, 1559, 1419, 1364, 1168 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9 H), 2.77 (s, 3 H), 7.10 (t, J = 4.7 Hz, 1 H), 7.79 (d, J = 7.7 Hz, 1 H), 8.47 (d, J = 4.4 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3, 30.8 (isomer), 31.0, 47.7, 120.9, 123.0 (isomer), 128.5, 144.7 (isomer), 146.0, 149.0, 156.3 (isomer), 163.7. HRMS calcd. for $C_{10}H_{16}NS$ $(M+H)^+$: 182.1003. Found: 182.1006 $(M+H)^+$.

EXAMPLE 3

2-[(3-*tert*-Butylsulfanyl)pyridin-2-ylmethylsulfanyl]ethylamine (5)

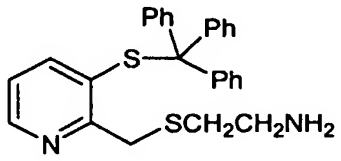


To a three-necked flask equipped with a mechanical stirrer was added THF (200 mL), *n*-BuLi (17.4 mL, 43.5 mmol, 2.5 M in hexane) and isopropylamine (5.7 mL, 43.5 mmol) at -78 °C. After 30 minutes, compound **4** (7.1 g in 20 mL THF, 39.5 mmol) was added dropwise. After stirring for 15 minutes, cystamine **(2)** (7.2 g in 20 mL DME, 47.3

mmol) was added in one portion. The mixture was warmed to rt slowly and stirred overnight. It was poured into water (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed *in vacuo*. The residue was bulb-to- bulb distilled (150 °C, 0.5 mmHg) to afford 7.5 g (75%) of the desired product as a brown liquid. FTIR (thin film) 3357, 2961, 1560, 1458, 1364 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 9 H), 2.66 (t, J = 6.2 Hz, 2 H), 2.88 (t, J = 6.2 Hz, 2 H), 4.20 (s, 2 H), 7.16 (dd, J = 7.7, 4.7 Hz, 1 H), 7.83 (d, J = 7.8 Hz, 1 H), 8.53 (d, J = 4.6 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.2, 36.2, 36.3, 41.3, 47.9, 121.9, 128.6, 146.1, 149.3, 163.6. HRMS calcd. for $C_{12}H_{21}N_2S_2$ $(M+H)^+$: 257.1146. Found: 257.1143 $(M+H)^+$.

EXAMPLE 4

2-[3-(Triphenylsulfanyl)pyridin-2-ylmethylsulfanyl]ethylamine (6)



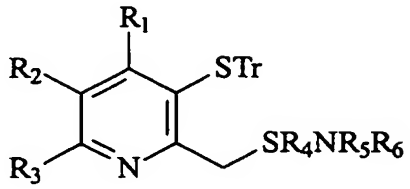
To an argon purged flask was added compound **5** (0.36 g, 1.40 mmol), methanesulfonic acid (2 mL) and acetic acid (4 mL). The mixture was heated to reflux for 20 h and then the solvent was removed *in vacuo*. The residue was dissolved in dichloromethame (20 mL) and triphenylmethanol (0.44 g, 1.68 mmol) was added. After stirring at rt for 1 h, the mixture was poured into aqueous $NaHCO_3$ with caution and then extracted with dichloromethane (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was purified by radial PLC (methanol) to afford 0.52 g (85%) of the desired product as a thick white oil. FTIR (thin film) 3363, 3055, 1599, 1489 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.93 (br s, 2 H), 2.51 (m, 2 H), 2.75 (m, 2 H), 3.48 (s, 2 H), 6.70 (m, 1 H), 7.12-7.37 (m, 16 H), 8.19 (d, J = 4.1 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.1, 35.5, 41.0, 71.6, 121.4, 126.9, 127.0,

127.2, 127.8, 129.8, 130.7, 141.6, 143.6, 147.4, 161.5. HRMS calcd. for $C_{27}H_{26}N_2S_2$: 443.1616 $(M+H)^+$. Found: 443.1618 $(M+H)^+$.

The foregoing is illustrative of the present invention, and is not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein.

THAT WHICH IS CLAIMED IS:

1. A method of making a compound of **Formula VI:**



(VI)

wherein:

Tr is a triphenyl group;

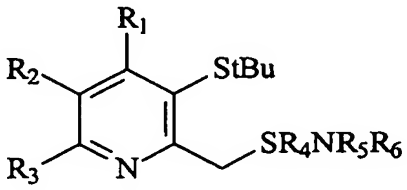
R_1, R_2 and R_3 are each independently selected from the group consisting of H, C1-C4 alkyl, C1-C4 alkoxy, aryl, heteroaryl, and arylalkyl;

R_4 is C2-C6 alkyl, and

R_5 and R_6 are each independently H or C1-C4 alkyl,

comprising:

reacting a compound of **Formula V**:



(V)

with Tr-OH to produce a compound of **Formula VI.**

2. A method according to claim 1, wherein said reacting step is carried out in the presence of a strong organic acid.

3. A method according to claim 1, wherein said reacting step is carried out in the presence of an acid selected from the group consisting of methanesulfonic acid and arylsulfonic acid.

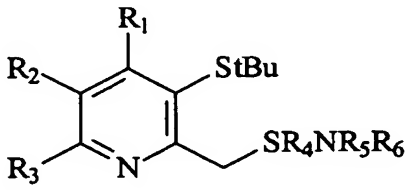
4. A method according to claim 1, wherein said reacting step is carried out in a polar solvent.

5. A method according to claim 1, wherein said reacting step is carried out in acetic acid.

6. A method according to claim 1, wherein said reacting step is carried out at room temperature.

7. A method according to claim 1, wherein said reacting step is a one-pot, two step reacting step.

8. A method of making a compound of **Formula V**:



(V)

wherein:

tBu is *tert*-butyl;

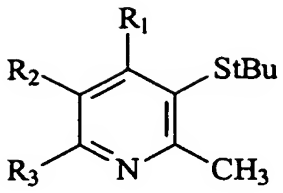
R_1, R_2 and R_3 are each independently selected from the group consisting of H, C1-C4 alkyl, C1-C4 alkoxy, aryl, heteroaryl, and arylalkyl;

R_4 is C2-C6 alkyl, and

R_5 and R_6 are each independently H or C1-C4 alkyl,

comprising:

reacting a compound of **Formula IV:**



(IV)

with $R_6R_5NR_4SSR_4NR_5R_6$ in the presence of a strong amide base to produce a compound of **Formula V.**

9. A method according to claim 8, wherein said reacting step is carried out in an etherial solvent.

10. A method according to claim 8, wherein said reacting step is carried out in a solvent selected from the group consisting of dialkyl ether, dimethoxyethane, tetrahydrofuran, or combinations thereof.

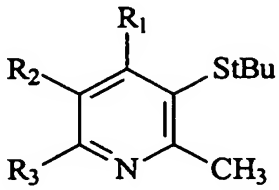
11. A method according to claim 8, wherein said strong amide base is selected from the group consisting of lithium, sodium, and potassium amide bases.

12. A method according to claim 8, wherein said amide base is a dialkyl amide base.

13. A method according to claim 8, wherein said reacting step is carried out at a temperature less than room temperature.

14. A method according to claim 8, wherein said reacting step is carried out at a temperature of from –80 to 0 degrees centigrade.

15. A method making a compound of **Formula IV**:



(IV)

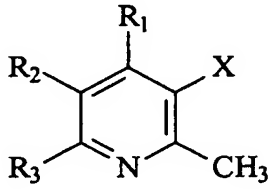
wherein:

tBu is *tert*-butyl; and

R_1, R_2 and R_3 are each independently selected from the group consisting of H, C1-C4 alkyl, C1-C4 alkoxy, aryl, heteroaryl, and arylalkyl;

comprising:

reacting a compound of **Formula III:**



(III)

wherein X is halogen, with sodium *tert*-butylthiolate or potassium *tert*-buthylthiolate to produce a compound of **Formula IV.**

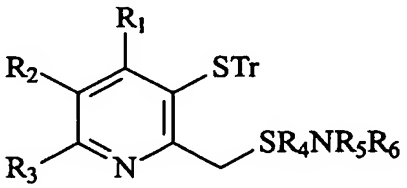
16. A method according to claim 15, wherein said reacting step is carried out in a polar aprotic solvent.

17. A method according to claim 15, wherein said reacting step is carried out in a nonaqueous solvent.

18. A method according to claim 15, wherein said reacting step is carried out in a solvent selected from the group consisting of dimethylformamide and dimethylsulfoxide.

19. A method according to claim 15, wherein said reacting step is carried out at a temperature of from 20 to 130 degrees centigrade.

20. A compound of Formula VI:



(VI)

wherein:

Tr is a triphenyl group;

R_1, R_2 and R_3 are each independently selected from the group consisting of H, C1-C4 alkyl, C1-C4 alkoxy, aryl, heteroaryl, and arylalkyl;

R_4 is C2-C6 alkyl, and

R_5 and R_6 are each independently H or C1-C4 alkyl;

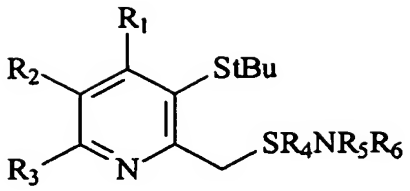
subject to the proviso that *(i)* R_1, R_2 and R_3 are not all simultaneously H, or *(ii)* R_4 is not C2, or *(iii)* R_5 and R_6 are not simultaneously H.

21. A compound according to claim 20, wherein R_1 R_2 and R_3 are H.

22. A compound according to claim 20, wherein R_4 is C2 alkyl.

23. A compound according to claim 20, wherein R_5 and R_6 are both H.

24. A compound of **Formula V**:



(V)

wherein:

tBu is *tert*-butyl;

R_1, R_2 and R_3 are each independently selected from the group consisting of H, C1-C4 alkyl, C1-C4 alkoxy, aryl, heteroaryl, and arylalkyl;

R_4 is C2-C6 alkyl, and

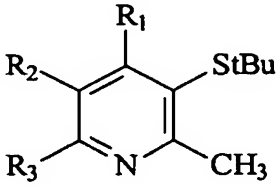
R_5 and R_6 are each independently H or C1-C4 alkyl.

25. A compound according to claim 24, wherein R_1 R_2 and R_3 are H.

26. A compound according to claim 24, wherein R_4 is C2 alkyl.

27. A compound according to claim 24, wherein R_5 and R_6 are both H.

28. A compound of **Formula IV**:



(IV)

wherein:

tBu is *tert*-butyl; and

R_1, R_2 and R_3 are each independently selected from the group consisting of H, C1-C4 alkyl, C1-C4 alkoxy, aryl, heteroaryl, and arylalkyl.

INTERNATIONAL SEARCH REPORT

Inte[illegible]onal Application No
PCT/US 02/17027

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 21623 A (MICROCIDE PHARMACEUTICALS INC) 29 March 2001 (2001-03-29) cited in the application	20-23
A	page 50 -page 51; claim 1	1-19, 24-28

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 September 2002	27/09/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Johnson, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter[illegible]onal Application No
PCT/US 02/17027

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0121623 A	29-03-2001	AU 7709500 A	24-04-2001
		BR 0014230 A	21-05-2002
		CZ 20020993 A3	17-07-2002
		EP 1222194 A1	17-07-2002
		NO 20021416 A	22-05-2002
		WO 0121623 A1	29-03-2001